REMARKS

Claims 59-70, 72-74, 76, 80-84, 88-92, 96-110 remain in this application.

Claims 71, 77-79, 85-87 and 93-95 have been cancelled. Claims 100-110 are new. Claims 59-70, 76, 80, 83, 84, 88, 91, 98 and 99 are currently amended.

Claims 59, 76 and 80 have been amended to specify that the conditionally lethal first gene is selected from the group consisting of a gene encoding indoleacetamide hydrolase (IAMH), a gene encoding isopentyltransferase, a gene encoding methoxinine dehydrogenase, a gene encoding rhizobitoxine synthase, and a gene encoding phosphonate monoester hydrolase. These are all known conditionally lethal genes that are described in the specification at page 26, lines 5-31 and for which appropriate literature references are there provided. Applicants note that the previous reference in the claims to "oncogene 2" and "oncogene 4" have been replaced with, respectively, references to a gene encoding indoleacetamide hydrolase (IAMH) and a gene encoding isopentyltransferase, which are the enzymes encoded by oncogenes 2 and 4 of *Agrobacterium*, also as described at page 26 of the specification.

Claims 59, 76 and 80 have also been amended to recited that the second gene that confers a non-naturally occurring trait of interest on the plant is selected from the group consisting of

(a) a gene which, when expressed in said plant cell, confers insect resistance on said plant cell;

(b) a gene which, when expressed in said plant cell, confers an output trait on said plant cell;

(c) a gene encoding an industrially useful enzyme;

(d) a gene encoding a pharmaceutically active compound;

(e) a gene encoding rennin or hirudin; and

(f) a gene encoding an antisense RNA.

Basis for this amendment is found in, e.g. claims 61-66 of record and in the specification from page 1, line 15 through page 4, line 3.

Consequential amendments have been made in the dependent claims, in view of the above-discussed amendments concerning the first and second genes.

Also, new dependent claims 100-110 have been added, which are parallel to presently amended claims 60-72. Applicants respectfully submit that these amendments do not constitute new matter.

A number of minor amendments, made for the purposes of clarification only, are discussed below in connection with the rejections raised under 35 USC § 112, second paragraph.

Concerning 35 USC § 112, Second Paragraph

Claims 69-70, 83-84, 88-92 and 96-98 of record stand rejected under 35 USC § 112, second paragraph as being indefinite.

The rejection of claims 69-70 as lacking antecedent basis for the expression "said particular plant" is obviated by the present amendment of the claims to delete "particular".

Claims 83, 88 and dependents stand rejected as being indefinite for inclusion of the expression "or a related derivative" on the grounds that the degree of relatedness or structural similarity is unclear. Accordingly, the claims have been amended to recite that the derivative is an auxin derivative that is a substrate for IAMH. Exemplary auxin derivatives that are substrates for IAMH are discussed in the specification as e.g. page 15 lines 1-26, and the skilled person will understand what is meant by this expression.

The rejection of claim 91 as being indefinite for lack of antecedent basis and claim 88 for the expression "the auxin transport inhibitor" is obviated by the present amendment of claim 91 to depend upon claim 89 as suggested by the Examiner.

Concerning 35 USC § 112, First Paragraph

Claims 59-67, 69-74, 76, 80-84, 88-92 and 96-99 of record stand rejected under 35 USC § 112, first paragraph, as lacking written description and enablement for use of a conditionally legal gene other than oncogene 2 of *Agrobacterium tumefaciens*.

Applicants respectfully traverse this rejection and submit that the subject matter of the claims, as presently amended, is fully described and enabled by the instant specification.

As discussed above, the claims have been amended to specify that the conditionally lethal first gene is selected from the group consisting of a gene encoding indoleacetamide hydrolase (IAMH), a gene encoding isopentyltransferase, a gene encoding methoxinine dehydrogenase, a gene encoding rhizobitoxine synthase, and a gene encoding phosphonate monoester hydrolase. These are conditionally lethal genes that are known in the art, and which are described in the instant specification with appropriate literature references at page 26 lines 5-31.

The Examiner has cited both *University of California v. Eli Lilly and Co.* 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 (Fed. Cir. 1991) in support of the rejection of the claims for lack of written description. Applicants respectfully submit that the facts of the instant case are readily distinguishable from both *Eli Lilly* and *Amgen*. Both *Eli Lilly* and *Amgen* concerned claims drawn broadly to chemical compounds that had not yet been obtained and represented only hoped for future results. It was not possible to provide a written description of subject matter that had not yet been invented.

Specifically, in *Eli Lilly*, the court held that disclosure of rat insulin-encoding cDNA did not provide adequate written description of claims generally reciting cDNA encoding vertebrate insulin and mammalian insulin. The single species of vertebrate or mammalian cDNA disclosed did not describe the entire genus of vertebrate or mammalian cDNA's claimed.

In *Amgen*, at issue was an allegation of prior invention under 35 USC § 102(g) of a claim directed to a "purified and isolated DNA sequence" encoding human EPO. At the relevant time, the amino acid sequence for EPO was uncertain, and the gene

encoding it had not been cloned or sequenced. At issue was whether one Fritsch was first to conceive of purified and isolated human EPO based on a probing strategy of using two sets of fully degenerate cDNA probes of two different regions of the EPO gene to screen a gDNA library, which was the strategy that eventually resulted in successful identification and isolation of the EPO gene. The court held that, although Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even an idea of a possible method of obtaining it, he did not conceive a purified and isolated DNA sequence encoding EPO at the time, because he neither knew the structure or physical characteristics of it. The court held that "conception of a generalized approach for screening a DNA library that might be used to identify and clone the EPO gene of then unknown constitution is not conception of a 'purified and isolated DNA sequence' encoding human DNA".

The instantly claimed invention is thus readily distinguishable from both *Eli Lilly* and *Amgen*. The instant Applicants do not purport to claim unknown compounds that have not yet been invented and therefore cannot be adequately described other than by hoped for properties. Rather, Applicants claims recite, merely as one element of a novel and inventive combination, a conditionally lethal first gene selected from a group of conditionally lethal genes specifically described in the specification, for which the structure and physical characteristics are known in the art. Accordingly, Applicants respectfully submit that the specification provides a full and adequate written description of the conditionally lethal genes recited in the instant claims.

Concerning enablement, the Examiner contends that the use of oncogenes to cause a conditionally lethal phenotype is unpredictable and that undue experimentation would have been required by one of skill in the art to identify, isolate or evaluate a multitude of non-exemplified conditionally lethal genes including non-*Agrobacterium tumefaciens* oncogene 2.

Applicants respectfully traverse this rejection and submit that the conditionally lethal first genes recited in the claims, as presently amended, are fully enabled by the instant application as filed.

Applicants first respectfully submit that the Examiner's contentions concerning lack of enablement do not comport with and are indeed directly contradicted by the very

references that have been cited for lack of novelty. For instance, the Examiner asserts (page 9, second paragraph of the Office Action) that U.S. Patent No. 5,254,801 to Dotson *et al.* teaches use of the conditionally lethal phosphonate monoester hydrolase gene, which is one of the genes recited in claim 71 of record, and which is now recited in independent claims 59, 76 and 80. If it is the Examiner's position that the prior art enables the use of the conditionally lethal phosphonate monoester hydrolase gene, then it must be acknowledged that use of a gene encoding phosphonate monoester hydrolase is enabled by the later-filed instant application.

Similarly, U.S. Patent No. 5,278,057 to Jorgensen, also cited by the Examiner for lack of novelty, recites in, e.g. claim 13, a conditionally lethal gene encoding rhizobitoxine synthase, as recited in the instant specification and claims.

Furthermore, the Examiner states (page 10 last paragraph of the Office Action) that WO 97/40179 to Pioneer teaches the IAMH gene. Pioneer mentions at page 9, lines 15-30 that although one source of the enzyme IAMH is *Agrobacterium tumefaciens*, other sources are available, such as the IAMH gene from *Pseudomonas savastanoi.* Thus, the very reference cited by the Examiner discloses different sources for a gene encoding IAMH.

Hence, Applicants respectfully submit that if the above-mentioned conditionally lethal genes are sufficiently enabled for the purposes of a prior art rejection, then they must also be enabled with respect to the instant application.

The Examiner cites a number of literature references in connection with the rejections for lack of enablement.

The Examiner states that Smigocki *et al.* (1988) PNAS (U.S.A.) 85:5131-5135 teach (e.g. page 5131, Abstract) that plant transformation with a genetic construct comprising the *Agrobacterium tumefaciens* oncogene 4 sequence ligated to a strong constitutive promoter resulted in increased shooting and cell culture proliferation rather than any type of lethality. Applicants respectfully submit that the teachings of Smigocki *et al.* do not detract from enablement of the instant invention. Complete lethality is not required in many embodiments of the invention. Indeed, claim 88, as currently amended, specifies a sub-lethal auxin over-production phenotype for visually identifying a transgenic plant cell. In accordance with the teachings of the

instant specification, the skilled person can effect lethality in a plant or a sub-lethal phenotype, as desired. Rather than detracting from the enablement of the present invention, Smigocki *et al.* corroborate Applicants' assertion that oncogene 4 of *Agrobacterium* can be used in Applicants' methods of producing transgenic plants that can be identified visually and non-destructively.

The Examiner states that Medford *et al.* (1989) The Plant Cell 1:403-413 teach that the expression of a genetic construct comprising a heat-inducible heat-shock promoter ligated to *ipt* gene unpredictably did not change whether or not the heat-shock promoter was actually induced (see e.g. page 403, Abstract). Applicants respectfully submit that the findings of Medford *et al.* are ultimately inconclusive. At, e.g. page 405, second column and 407, second column, Medford *et al.* note that "leakiness" of the *ipt* gene at the control (uninduced) temperature resulted in a three to seven fold increase in cytokinin levels. As stated in the Abstract, this uninduced cytokinin increase affected various aspects of development in the control plants. In tobacco, these effects included release of axillary buds, reduced stem and leaf area, and an undeveloped root system. Hence, even in the uninduced state, there was cytokinin over production, presumably as a result of expression of the chimeric *ipt* gene.

The Examiner cites Kriete *et al.* (1996) The Plant Journal, 9(6):809-818 as evidence that the use of topical plant application of chemicals to induce conditionally lethal genes is unpredictable. The Examiner states that Kriete *et al.*, page 815, column 1 teach that most chemicals which are allegedly non-toxic precursors of toxins either are in fact phytotoxic or do not persist in the field environment, wherein the precursors when applied to plants transgenic for an enzyme-encoding gene are able to be converted into the toxic form, thus effecting a conditionally lethal phenotype.

Applicants respectfully disagree with this analysis of Kriete *et al.* Kriete *et al.'s* discussion of their own findings speaks very favourably to the use of induction of conditionally lethal genes with non-phytotoxic compounds. As discussed by Kriete *et al.* at the paragraph bridging pages 814-815, they found that the compound *N*-ac-Pt was a non-phytotoxic compound that destroyed plant tissues upon conversion to herbicide Pt in transgenic plants by the *E. coli argE* gene product. Moreover, in the same passage, Kriete *et al.* state that *N*-ac-Pt is non-phytotoxic up a dosage which is 100 times higher than required and remains unchanged for more than 14 weeks in

unmodified plants. They therefore conclude that the compound *N*-ac-Pt may be applied in high concentrations in the early growing season of the crop and should still be present in sufficient amounts at the time the *argE* gene product is expressed. Thus, clearly, *N*-ac-Pt was both non-phototoxic and persisted sufficiently in the field environment, for successful use for effecting a conditionally lethal phenotype.

Finally, the Examiner cites the instant specification, page 14, bottom paragraph through page 15, top paragraph and page 28, middle paragraph, as teaching that most chemically-activatable conditionally lethal genes have the disadvantage that they lead to cell death and plant lethality, thus preventing the recovery of a desired plant for further breeding, and that the *Agrobacterium tumefaciens* oncogene 2 is unique in its ability to affect a controllable-sub-lethal phenotype.

Applicants respectfully submit that the instant specification must be read as a whole, and that the specification specifically states, at page 26, lines 5-31, that the conditionally lethal genes recited in the presently amended claims are useful in the methods of the invention as presently claimed.

In view of the foregoing, reconsideration and withdrawal of the rejections of the claims under 35 USC § 112, first paragraph, are respectfully requested.

Concerning 35 USC § 102

Claims 59-60, 64-65, 69-70, 73-74 and 76 stand rejected under 35 USC § 102(b) as being anticipated by Dotson *et al.* (U.S. Patent No. 5,254,801).

Claims 59-60, 64-65, 67-70, 74, 76 and 80-84 stand rejected under 35 USC § as being anticipated by Jorgensen (U.S. Patent 5,278,057).

Claims 59-60, 64-70, 72-74 and 76 of record stand rejected under 35 USC § 102(b) as being anticipated by WO 97/40179 (Pioneer).

Claims 59-60, 64-70, 72-74, 76 and 80-84 stand rejected under 35 USC § 102(b) as being anticipated by Fabijanski *et al.* (U.S. Patent 5,426,041).

Applicants respectfully submit that the claims as presently amended, patentably distinguish from all of the cited references.

The Examiner cites Dotson *et al.* as teaching a second gene comprising a kamamycin resistance gene encoding a protein that confers the measurable phenotype of antibiotic resistance to a plant cell. Jorgensen and Fabijanski *et al.* are also cited for teaching a second gene that is a kamamycin resistance gene. Pioneer is cited for teaching a PAT gene conferring resistance to the herbicide bialaphos.

Independent claims 59, 76 and 80 have been amended to recite that the second gene is selected from the group consisting of:

(a) a gene which, when expressed in said plant cell, confers insect resistance on said plant cell;

(b) a gene which, when expressed in said plant cell, confers an output trait on said plant cell;

(c) a gene encoding an industrially useful enzyme;

(d) a gene encoding a pharmaceutically active compound;

(e) a gene encoding rennin or hirudin; and

(f) a gene encoding an antisense RNA;

thereby excluding antibiotic and herbicide resistance genes. None of the cited references teach or suggest a second gene selected from the group set forth in the instantly amended claims, obviating the rejections under 35 USC 102.

Concerning 35 USC § 103

Claims 59-60, 64-65, 69-74, 76 and 80-82 of record stand rejected under 35 USC § 103(a) as being unpatentable over Dotson *et al.*

The amendments to the claims, as discussed above concerning 35 USC § 102 obviate the obviousness rejection of the claims over Dotson *et al.* Dotson *et al.* do not teach or suggest a second gene selected from the group now recited in independent claims 59, 76 and 80.

Claims 61-63 and 66 of record stand rejected over Dotson *et al.* in view of Goodman *et al.* (U.S. Patent No. 5,550,038).

Applicants respectfully traverse this rejection. As acknowledged by the Examiner, Dotson *et al.* are silent on the use of plants as bioreactors. Indeed, Dotson *et al.* are concerned principally with selectively inducing male sterility in plants. Dotson *et al.* are silent on the use of conditionally lethal genes to identify transgenic plants encoding a non-naturally occurring trait of interest or to remove them from a growing environment as instantly claimed. The mention in Dotson of a kamamycin resistance gene, excluded from the presently amended claims, concerns the use of the kamamycin resistance gene as a marker for identifying or selecting cells in culture, and not as a "non-naturally occurring trait of interest" as that term is used in the instant claims and would be understood by a skilled person, in the context of the invention. There is certainly no suggestion in Dotson *et al.* to use transgenic plants as bioreactors to produce kamamycin.

Goodman *et al.* mention typical screening or selection markers for plant cells in culture such as antibiotic-resistance genes (paragraph bridging columns 3 and 4) but are absolutely silent with respect to conditionally lethal genes or their use.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because there is no suggestion or motivation to combine the teachings of these references. As mentioned above, there is nothing within the references themselves to suggest the necessary combination. Moreover, the Examiner has not provided any convincing line of reasoning as to why the skilled person would have been motivated to combine these references. Although Goodman *et al.* teach the use of antibiotic resistance genes for selecting an expression construct in culture, this is well known technology, and there is no specific or even general suggestion that it would be advantageous to use conditionally lethal genes as instantly claimed. The mere fact that these references *could* be combined or modified does not render the claimed combination obvious, because the references do not suggest the desirability of the instantly claimed combination. *In re Mills* 916 F.2d 680, 16 USPQ 2d 1430 (Fed. Cir. 1990). Mere hindsight based on Applicants' own disclosure is insufficient to establish a *prima facie* case of obviousness.

Claims 88, 92 and 96-98 stand rejected under 35 USC § 103(a) as being unpatentable over Fabijanski *et al.* in view of Dotson *et al.*

Applicants respectfully traverse this rejection and submit that the claims, as presently amended, patentably distinguish from Fabijanski *et al.* and in view of Dotson *et al.*

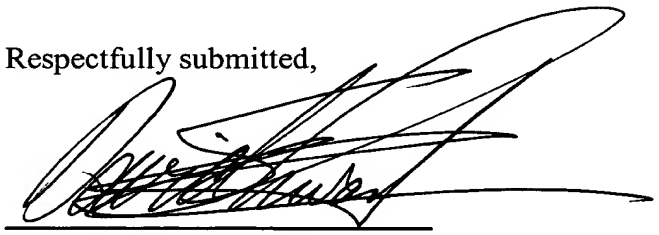
Claim 88 and the claims dependent thereon have been amended to recite the step of "visually identifying the at least one transgenic plant cell by its expression of a sub-lethal auxin-over production phenotype". Both Dotson *et al.* and Fabijanski *et al.* are concerned with creating male sterile plants, in which the conditionally lethal gene is used to kill plant cells or plant organs involved in plant fertility. There is no teaching or suggestion in either reference to use the conditionally lethal genes to express a sub-lethal phenotype, as instantly claimed.

Reconsideration and withdrawal of the rejections of the claims under 35 USC 103 are therefore respectfully requested.

In view of all of the foregoing, entry of the amendments and further consideration of this application, leading to its timely allowance, are respectfully requested.

Applicants acknowledge the Examiner's finding that claims 71, 89-91 and 99 of record are free of the prior art.

Respectfully submitted,



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